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## PEDIATRIC HIGHLIGHT

# Genetic influences on the difference in variability of height, weight and body mass index between Caucasian and East Asian adolescent twins

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**Objective:** Twin studies are useful for investigating the causes of trait variation between as well as within a population. The goals of the present study were two-fold: First, we aimed to compare the total phenotypic, genetic and environmental variances of height, weight and BMI between Caucasians and East Asians using twins. Secondly, we intended to estimate the extent to which genetic and environmental factors contribute to differences in variability of height, weight and BMI between Caucasians and East Asians.

**Design:** Height and weight data from 3735 Caucasian and 1584 East Asian twin pairs (age: 13–15 years) from Australia, China, Finland, Japan, the Netherlands, South Korea, Taiwan and the United States were used for analyses. Maximum likelihood twin correlations and variance components model-fitting analyses were conducted to fulfill the goals of the present study.

**Results:** The absolute genetic variances for height, weight and BMI were consistently greater in Caucasians than in East Asians with corresponding differences in total variances for all three body measures. In all 80 to 100% of the differences in total variances of height, weight and BMI between the two population groups were associated with genetic differences.

**Conclusion:** Height, weight and BMI were more variable in Caucasian than in East Asian adolescents. Genetic variances for these three body measures were also larger in Caucasians than in East Asians. Variance components model-fitting analyses indicated that genetic factors contributed to the difference in variability of height, weight and BMI between the two population groups. Association studies for these body measures should take account of our findings of differences in genetic variances between the two population groups.

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**Keywords:** height; weight; BMI; population group; twins; genes

### Introduction

Height, weight and body mass index (BMI, kg/m<sup>2</sup>) are multifactorial traits determined by multiple genes and

environmental factors and their interactions. Genes for these body measures are known to act through endocrine systems, hormones, metabolism, calcium and phosphate homeostasis and other mechanisms.<sup>1</sup> Twin studies have generally found heritability estimates of 0.85–0.90 for height,<sup>2</sup> approximately, 0.70 for weight<sup>3</sup> and 0.75–0.85 for BMI<sup>4–6</sup> in adolescents and adults; small shared environmental influences have been reported for height in some populations but rarely for weight and BMI. As most twin

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studies to date have been carried out with Caucasian samples, genetic and environmental contributions to the variations of height, weight and BMI among East Asian populations are less well known. A few existing studies using Chinese and Japanese twins suggested the importance of genetic factors in height, weight and BMI.<sup>7,8</sup> However, these studies were all based on small samples. Recently, Hur<sup>9</sup> examined 888 pairs of South Korean adolescent twins and found that 82 and 87% of the total variances of BMI were associated with genetic factors for males and females, respectively, with the remaining variances being attributable to nonshared environmental factors including measurement error. These results suggest that heritability estimates of body size in East Asian populations may be similar to those found in Caucasian populations.

Even if relative contributions of genes and environments to the total phenotypic variances of height, weight and BMI are similar in Caucasian and East Asian populations, the absolute variances of genetic and environmental factors for the body measures can differ appreciably between the two major human populations. For example, higher stature and BMI have been consistently found in Caucasian populations as compared with East Asian populations.<sup>10</sup> This may be partly because of genetic differences. However, cultural variations in lifestyle factors like physical activities, exercise patterns and dietary habits can also lead to differences in means and variations of height, weight and BMI between Caucasian and East Asian populations.

Although numerous twin studies of height, weight and BMI have been conducted, most of these have primarily examined genetic and environmental variations within a population. Only a few twin studies examined the differences in genetic and environmental variances of body measures among different human populations. Allison *et al.*<sup>11</sup> reanalyzed BMI in 126 pairs of African-American and 112 pairs of European-American adolescent twins originally published by Osborne<sup>12</sup> and found that the absolute variances of genetic and environmental influences (hence, the total phenotypic variance) were greater in African-American twins than in European-American twins, although heritability estimates of BMI were similar in the two population groups (93 and 91%). Given the high heritability estimates, the results of the Allison *et al.*<sup>11</sup> study suggest that the difference in the phenotypic variance of BMI between African Americans and European Americans may be largely genetic in origin.

Recently, Hur *et al.*<sup>13</sup> compared the variability of birth weight between Caucasian and East Asian populations using twin data collected from three Caucasian countries (Australia, the Netherlands, and the United States) and two East Asian countries (Japan and South Korea). Hur *et al.*<sup>13</sup> found that the total variance in birth weight was significantly larger in Caucasian than in East Asian samples, and that the difference was largely because of the difference in the intrauterine environmental variance in birth weight between the Caucasian and East Asian sample. Given that the female pre-pregnancy weight has been shown to be a strong predictor of

birth weight<sup>14</sup> and that various maternal genes have been shown to influence fetal growth,<sup>15</sup> Hur *et al.*<sup>13</sup> speculated that the difference in the intrauterine environmental variance in birth weight between Caucasians and East Asians found in their study might reflect the difference in the genetic variance of BMI in females between the two population groups.

In this study, we compared genetic and environmental variances of height, weight and BMI in Caucasian and East Asian populations using adolescent twin data collected from four Caucasian countries (Australia, Finland, the Netherlands and the USA) and four East Asian countries (China, Japan, South Korea and Taiwan). We address two research questions in this study: (1) Are there differences in the total phenotypic variances in height, weight and BMI between Caucasian and East Asian adolescents?; and (2) if there are any, are the observed differences in the total phenotypic variances in height, weight and BMI between these two major human populations determined genetically and/or environmentally? In answering these questions, we attempted to decompose differences in the total phenotypic variances in height, weight and BMI between the two population groups into genetic and environmental components, and estimated the relative contributions of these factors.

## Methods

### *Samples and measures*

Table 1 presents the number of twin pairs, mean age and birth years of the twin participants broken down by country, zygosity and population group. In total, data from 1584 pairs of East Asian and 3735 pairs of Caucasian twins were analyzed in this study. Twins in the Caucasian group comprised 793 monozygotic male (MZM), 647 dizygotic male (DZM), 880 monozygotic female (MZF), 646 dizygotic female (DZF) and 769 opposite-sex dizygotic (OSDZ) complete pairs; those in the East Asian group consisted of 475 MZM, 146 DZM, 562 MZF, 151 DZF and 250 OSDZ complete pairs. In all four East Asian countries, the number of DZ twins was consistently smaller than that of MZ twins. This was in line with lower DZ twin birth rates in Asians,<sup>16,17</sup> and does not entirely represent an ascertainment bias. The total sample ranged from 13 to 15 years of age, with a mean age of 14.1 years (s.d. = 0.4) for Caucasians and 14.0 years (s.d. = 0.7) for East Asians. For all samples, BMI (kg/m<sup>2</sup>) was calculated from weight (kg) and height (m), including measured and/or self-reported, as described below.

Although birth years of the twins varied across countries, overall, they were similar in Caucasian and East Asian samples. The birth years ranged from 1975 to 1993 for Caucasian twins, and from 1968 to 1994 for East Asian twins. We examined cohort effects on height, weight and BMI in our samples and found them to be minimal (see below).

**Australia.** Australian twin pairs were collected as part of an ongoing study on melanoma risk factors.<sup>18</sup> Twins were

**Table 1** The number of pairs, mean (s.d.) age, and birth years of twins by zygosity, country and population group<sup>a</sup>

	East Asians					Caucasians				
	CH	JP	KO	TW	Total	AU	FIN	NL	USA	Total
MZM	47	177	222	29	475	140	224	139	290	793
Age in years	14.2 (0.8)	14.0 (0.6)	14.1 (0.7)	13.9 (0.7)	14.1 (0.6)	14.0 (0.0)	14.0 (0.0)	14.2 (0.6)	14.4 (0.6)	14.2 (0.5)
DZM	17	52	68	9	146	126	248	112	161	647
Age in years	13.9 (0.7)	14.0 (0.7)	14.1 (0.6)	13.7 (0.8)	14.0 (0.7)	14.0 (0.0)	14.0 (0.0)	14.1 (0.5)	14.3 (0.5)	14.1 (0.4)
MZF	62	230	237	33	562	142	245	206	287	880
Age in years	13.9 (0.9)	14.0 (0.6)	14.1 (0.6)	13.9 (0.8)	14.0 (0.7)	14.0 (0.0)	14.0 (0.0)	14.1 (0.6)	14.3 (0.6)	14.1 (0.5)
DZF	13	61	69	8	151	124	207	140	175	646
Age in years	14.0 (0.9)	14.0 (0.7)	14.0 (0.6)	14.3 (0.9)	14.0 (0.7)	14.0 (0.0)	14.0 (0.0)	14.1 (0.6)	14.3 (0.6)	14.1 (0.4)
OSDZ	31	107	101	11	250	207	362	200	0	769
Age in years	14.0 (0.8)	13.9 (0.7)	14.0 (0.7)	13.4 (0.7)	14.0 (0.7)	14.0 (0.0)	14.0 (0.0)	14.3 (0.6)		14.1 (0.3)
Total	170	627	697	90	1584	739	1286	797	621	3735
Age in years	14.0 (0.8)	14.0 (0.7)	14.1 (0.6)	13.9 (0.8)	14.0 (0.7)	14.0 (0.0)	14.0 (0.0)	14.2 (0.6)	14.2 (0.6)	14.1 (0.4)
Birth years	1991–1993	1968–1985/1991–1993	1990–1994	1970–1973	1968–1994	1978–1992	1983–1987	1975–1978/1990–1992	1978–1993	1975–1993

Abbreviations: AU, Australia; CH, China; DZF, dizygotic female twins; DZM, dizygotic male twins; FIN, Finland; JP, Japan; KO, South Korea; MZF, monozygotic female twins; MZM, monozygotic male twins; NL, the Netherlands; OSDZ, opposite-sex dizygotic twins; TW, Taiwan. <sup>a</sup>For the Australian and Finnish samples, only twins of age 14 years were used in the present study.

recruited by contacting principals of primary schools in the greater Brisbane area, through word of mouth and by media appeals. The twins who registered their interest were contacted and participation was conditional upon the informed consent of the twins and their parents. In total, 739 complete twin pairs at age 14 years were used in this study. To minimize age bias, measurements were taken as close as possible to the twins' fourteenth birthday. Height and weight were both measured clinically using a stadiometer and accurate scales respectively. As the birth years of the twins varied widely (1978 to 1992), we computed correlations between birth years and height, weight and BMI. The correlations were very modest ( $r=0.06$ – $0.08$ ), suggesting that birth year cohort effects on the three body measures were minimal. Zygosity of same-sex adolescent twins was determined using DNA markers.

**China.** Chinese twins were drawn from the Guangzhou twin registry (GTR).<sup>19</sup> The GTR is a population-based registry established to study genetic etiology of ophthalmic diseases using the twins born in the greater Guangzhou area. In 2006, 705 pairs of the twins aged 7 to 15 years living in the districts close to the Zhongshan University were invited to the Zhongshan Ophthalmic Center for the eye and other medical examinations. Of those invited, 170 pairs aged between 13 and 15 years old were chosen for this study. These twins' height and weight were measured at Zhongshan Ophthalmic Center. Zygosity for the twins invited was determined using DNA markers.

**Finland.** The Finnish sample is part of the FinnTwin12 longitudinal study of behavioral development and health habits inception in 1994.<sup>20</sup> All twins in the Finnish birth cohorts spanning 1983–1987 were ascertained from the Nation's Central Population Registry. The initial self-report survey including questions regarding current height and weight was mailed to the twins when they reached ages 11

and 12 years. The follow-up surveys were mailed to the twins when they reached ages 14 and 17.5 years, respectively. Only those twin pairs in which both members of the pair reported their height and weight at 14 years were included in the present analyses (1286 twin pairs). The response rate at age 14 years was 89.8%. No significant effects of birth year on mean height or weight were observed.

Zygosity was determined by a validated questionnaire method<sup>21</sup> supplemented by information from parents, and in some cases by photographs and DNA marker tests.

**Japan.** Japanese twins consisted of 627 pairs drawn from two sources: One from a twin database built in the secondary school attached to the University of Tokyo<sup>22</sup> and the other one from The Tokyo Twin Cohort Project (ToTCoP).<sup>23</sup> The first source included 195 pairs of twins at age 14 years who underwent health examination at the secondary school attached to the University of Tokyo. Height and weight for these twins were measured during the health examination. Zygosity of these twins was determined using DNA markers. Although the twins in this sample were all 14 years old, because the span of their birth years was large (1968–1985), we computed correlations between birth years and three body measures. However, the correlations were negligible ( $r=-0.04$ – $0.02$ ), suggesting that birth year cohort effects on body measures in this period were minimal. For this study, the ToTCoP provided an additional 432 pairs of twins aged between 13 and 15 years. Height and weight for these twins were self-reported through a mail survey. Zygosity of the twins in the ToTCoP sample was determined using the questionnaire method.<sup>24</sup> The birth years of the ToTCoP sample ranged from 1991 to 1993. We selected 14-year-old twins from the ToTCoP sample and the secondary school twin sample and compared their means for height, weight and BMI. No significant differences were found in any of the three body measures.

*The Netherlands.* All Dutch participants were registered with the Netherlands Twin Registry, kept by the Department of Biological Psychology at the VU University in Amsterdam. Information on height and weight is obtained by a self-report. A total of 666 individuals took part in the Adult Twin Register Questionnaire collection in 1991, whereas the remaining individuals ( $n=928$ ) took part in the questionnaire research of the Young Netherlands Twin Register.<sup>25</sup> Zygosity in same-sex twin pairs was assessed by DNA or blood group polymorphisms or by a series of items on physical resemblance and confusion by family and strangers, answered by the mother of the twins. Twins in the Adult Twin Register Questionnaire part of the sample were born between 1975 and 1978; twins in the Young Netherlands Twin Register part of the sample were born in 1990 (87%), 1991 (12%) and 1992 (1%). Although there were large differences in birth years between the Young Netherlands Twin Register and Adult Twin Register Questionnaire sample, these two Dutch samples did not differ significantly in height, weight, or BMI, suggesting no birth year cohort effects.

*South Korea.* The South Korean twins were drawn from the South Korean Twin Registry (SKTR).<sup>26</sup> The SKTR is a nationwide volunteer twin registry that includes twins from infants to young adults. In early 2006, a survey including questions on current height and weight was mailed to adolescent and young adult twins living in Seoul and three counties in South Korea. The overall response rate of the mail survey in 2006 was somewhat over 30%. Of those who returned the survey, 310 pairs of twins fell in the 13 to 15 year age range. In addition to these twins, we obtained height and weight data from 387 twin pairs aged between 13 and 15 years as part of the regular SKTR telephone interview. The means for height, weight and BMI in the telephone and mail survey were not significantly different, suggesting that the method of data collection did not affect the results.

Zygosity of the twins in the SKTR was determined by the questionnaire method.<sup>24</sup> Although the questionnaire method is less accurate than DNA analysis, those twin pairs whose zygosity was ambiguous were excluded from data analyses. In this study, for example, 34 pairs were excluded because of uncertain zygosity.

*Taiwan.* Taiwanese twin pairs were participants of the Taipei Adolescent Twin/Sibling Family Study (TATSFS)<sup>27</sup> where twins were recruited from 51 junior high schools in Taipei. The overall participation rate was approximately 61%. Among those (370 pairs) who participated in the study, 90 pairs of twins aged between 13 and 15 years were selected for the present study. Zygosity of the twin pairs was determined by analyses of DNA markers. Height and weight data were self-reported.

*The United States.* The US sample consisted of 621 twin pairs aged between 13 and 15 years who participated in the Minnesota Twin Family Study (MTFS).<sup>28</sup> The MTFS is a longitudinal, population-based study of genetic and environ-

mental influences on substance abuse and related problems. The MTFS recruits twins born in Minnesota from birth records obtained through the Minnesota State Health Department, and therefore, twin participants of the MTFS are broadly representative of Minnesota preadolescent and adolescent children. Almost all the twins in the MTFS are Caucasians (over 95%). Twins' height and weight were measured by a trained staff when the twins visited the MTFS laboratories for a day-long in-person assessment. As the birth years of the twins varied from 1978 to 1993, we computed correlations between birth years and height, weight and BMI controlling for age. The correlations ranged from  $-0.04$  to  $0.07$ , suggesting that birth year cohort effects on the three body measures were negligible.

Zygosity was determined by the agreement of three estimates: (1) a standard zygosity questionnaire completed by parents, (2) evaluation by MTFS staff of physical similarity based on eye, hair, face and ear characteristics, and (3) similarity on fingerprint ridge count, cephalic index and ponderal index.<sup>29</sup> If the three estimates did not agree, a serological analysis was conducted using DNA markers.

## Analytic methods

To fulfill the goals of the present study, we examined descriptive statistics for height, weight and BMI, computed maximum-likelihood correlations for the five types of twins (MZM, DZM, MZF, DZF, and OSDZ) for each of the three body measures, and carried out variance components model-fitting analyses. To maximize the sample size for each twin group, twin data were pooled across countries within the Caucasian and East Asian sample before analyses. In both correlational and model-fitting analyses, age and country were treated as covariates to control for their main effects.

Using the raw data option in Mx,<sup>30</sup> we fit a sex-limitation model<sup>31</sup> to the data. In the full sex-limitation model, the total phenotypic variance of a trait was decomposed for both sexes into three sources: additive genetic (A), shared environmental (C) and nonshared environmental (E) variances. Measurement error is confounded with E. A represents the sum of the average effect of all alleles that influence a trait, and correlates at 1.0 for MZ and at 0.5 for same-sex DZ twins. For OSDZ twins, however, the correlation for A can be estimated between 0 and 0.50 if some of the additive genes for a trait are sex-specific. C reflects those environmental factors that the two members of a twin pair share. Examples of C include family socioeconomic status and nutrition shared in the family. C correlates 1.0 for both MZ and DZ twins. Finally, E, represents environmental factors that are unique to each member of a twin pair and measurement error. Examples of E include accidents and virus infection.

In the full sex-limitation model, A, C and E parameters were allowed to differ between the Caucasian and East Asian samples as well as between the two sexes.

Five steps were taken to identify the best-fitting model. First, a saturated model where all variances, covariances and means of the first- and second-born twins were allowed to vary was fit to the data. Secondly, the fit of the ACE model was compared with the saturated model. Third, additive genetic correlations for OSDZ twins were fixed to be 0.5 in the Caucasian and East Asian group to examine the presence of sex-specific genes. Fourth, we eliminated each of A and C from the full model to examine the significance of these parameters. Finally, A, C and E in each sex were equated across Caucasians and East Asians to determine population differences in A, C and E for height, weight and BMI. We decided to retain the variance parameter unless the parameter could be eliminated simultaneously from both Caucasian and East Asian groups, as the main purpose of this study was to compare genetic and environmental variances in Caucasian and East Asian adolescents.

The raw data option in Mx calculates two times the negative log-likelihood of the data. As the difference in negative log-likelihood between the two nested models is  $\chi^2$  distributed, the likelihood ratio  $\chi^2$  test was used to select the best-fitting model. A significant change in  $\chi^2$  from the full to the constrained model indicates that the constraint of the parameter is not acceptable; a nonsignificant change, on the other hand, suggests that the parameter should be removed to achieve parsimony of the model.

## Results

### Descriptive statistics

Table 2 provides means and variances for height, weight and BMI broken down by zygosity, country and population group. Whereas height was approximately normally distributed, the distributions of weight and BMI were significantly positively skewed and kurtotic. The values of weight and BMI were therefore log-transformed to obtain approximate normality.

**Effects of the population group.** The means and variances were significantly greater among Caucasian than among East Asian adolescents in both sexes for all three body measures, suggesting that phenotypic variations of height, weight and BMI are larger in Caucasians than in East Asians.

**Sex and age effects.** For height and weight, sex effects were significant for means and variances (males > females) in both population groups. BMI showed different patterns in two population groups, however; in Caucasians, females were slightly, but significantly greater than males for both the mean and variance, but in East Asians, the mean was equal in males and females, whereas the variance was significantly greater in males than in females.

Age effects were statistically significant but modest for all three body measures. The correlations of age with height,

**Table 2** Means (variances) for height (cm), weight (kg) and BMI by Zygosity, country and population group

Population	Country	Height				Weight				BMI			
		MZM	DZM	MZF	DZF	OSDZ	MZM	DZM	MZF	OSDZ	MZF	DZF	OSDZ
CAUC	AU	164.2 (79.2)	164.6 (75.7)	160.3 (49.0)	161.8 (43.6)	162.5 (47.6)	53.5 (116.6)	55.4 (169.0)	53.6 (146.4)	55.1 (116.6)	20.8 (15.2)	20.3 (13.7)	20.8 (11.6)
	FIN	164.2 (90.3)	164.4 (70.6)	161.1 (39.7)	161.5 (36.0)	163.4 (54.8)	52.4 (106.1)	52.6 (112.4)	50.3 (70.6)	52.3 (100.0)	19.3 (6.8)	19.4 (8.4)	19.3 (6.8)
	NL	171.4 (98.0)	173.0 (68.9)	166.8 (47.6)	167.6 (43.6)	169.6 (64.0)	55.8 (104.0)	56.6 (88.4)	53.9 (86.5)	54.3 (77.4)	18.8 (4.8)	18.8 (4.8)	18.9 (4.8)
	USA	170.6 (67.2)	171.4 (67.2)	163.5 (41.0)	164.1 (33.6)	166.1 (43.6)	62.6 (171.6)	63.9 (210.3)	58.5 (151.3)	61.9 (201.6)	21.4 (13.7)	21.6 (17.6)	22.9 (24.0)
East Asians	Total	167.8 (92.2)	167.7 (84.6)	163.1 (49.0)	163.6 (43.6)	164.7 (64.0)	56.9 (151.3)	56.7 (163.8)	54.3 (123.2)	55.0 (134.6)	20.1 (10.2)	20.0 (12.3)	20.5 (14.4)
	CH	165.7 (60.8)	165.2 (79.2)	155.8 (53.3)	154.2 (29.2)	159.1 (88.4)	52.4 (81.0)	50.0 (106.1)	46.7 (53.3)	48.2 (82.8)	19.0 (5.8)	18.2 (7.3)	18.7 (4.0)
	JP	162.6 (54.8)	163.2 (77.4)	155.6 (32.5)	155.9 (32.5)	158.0 (57.8)	51.4 (94.1)	49.3 (82.8)	46.2 (47.6)	46.6 (51.8)	19.3 (7.3)	18.4 (5.3)	19.1 (6.3)
	KO	167.9 (49.0)	167.0 (53.3)	159.6 (22.1)	159.5 (21.2)	163.4 (60.8)	55.5 (118.8)	55.0 (100.0)	49.9 (49.0)	52.8 (77.4)	19.6 (9.0)	19.7 (8.4)	19.4 (6.8)
Total	TW	164.3 (75.7)	162.6 (50.4)	156.5 (36.0)	158.8 (16.0)	160.2 (41.0)	54.0 (136.9)	50.6 (86.5)	49.3 (51.8)	50.9 (57.8)	19.8 (10.9)	19.0 (5.8)	20.1 (7.3)
	Total	165.5 (59.3)	165.2 (67.2)	157.4 (34.8)	157.6 (29.2)	160.4 (68.9)	53.6 (110.3)	52.1 (100.0)	48.0 (51.8)	49.5 (74.0)	19.5 (7.8)	19.0 (7.3)	19.2 (6.8)

Abbreviations: AU, Australia; CAUC, Caucasians; CH, China; DZF, dizygotic female twins; DZM, dizygotic male twins; FIN, Finland; JP, Japan; KO, South Korea; MZF, monozygotic female twins; MZM, monozygotic male twins; NL, the Netherlands; OSDZ, opposite-sex dizygotic twins; TW, Taiwan. Although weight and BMI values were log transformed for statistical analyses, non-transformed values are reported here.

weight and BMI were, respectively, 0.22, 0.22 and 0.14 in the East Asian and 0.27, 0.25 and 0.14 in the Caucasian group.

#### *Zygosity effects*

For height and weight, there were no significant variance or mean differences between MZ and DZ twins for both males and females in both population groups, suggesting no significant zygosity effects on height or weight. For BMI, however, variance was significantly larger in MZ than in DZ twins in male Caucasians, but not in female Caucasians or in any of the two gender groups in East Asians. The difference in variance between the two zygosity groups in male Caucasians was very modest, although it attained statistical significance. Means for BMI in both population groups for both sexes were not significantly different between the two zygosity groups, suggesting no zygosity effects on the mean level of BMI.

#### *Twin correlations*

Table 3 provides maximum likelihood correlations for height, weight and BMI for the five groups of twins in the Caucasian and East Asian group and their 95% confidence intervals. For both Caucasian and East Asian adolescents, MZ twin correlations were consistently much higher than DZ twin correlations in both sexes for all three body measures, suggesting substantial genetic influences on height, weight and BMI.

For height, same-sex DZ twin correlations were somewhat higher than half the MZ twin correlations in both sexes, indicating possible shared environmental effects. OSDZ twin correlations for height were much lower than same-sex DZ twin correlations in both population groups. These results suggested the existence of sex-specific genes for height.

Weight and BMI showed similar patterns of twin correlations. In Caucasians, same-sex DZ twin correlations were slightly higher than half the MZ twin correlations in both sexes, suggesting some influences of shared environmental factors. In East Asians, however, whereas male DZ twin correlations tended to suggest the existence of shared environmental factors, female DZ twin correlations indicated some hints of nonadditive genetic effects, as female DZ twin correlations were lower than half the MZ twin

correlations for both weight and BMI. OSDZ twin correlations for weight and BMI were similar to the female DZ twin correlations, but they were lower than male DZ twin correlations.

Overall, these patterns of twin correlations suggested that a genetic model with additive genetic (A), shared environmental (C) and nonshared environmental effects (E) was appropriate for height, weight and BMI in both population groups. Although East Asian females showed some hint of nonadditive genetic effects on weight and BMI, sample sizes for East Asian DZ twins were not sufficiently large to detect nonadditive genetic effects.

#### *Model-fitting*

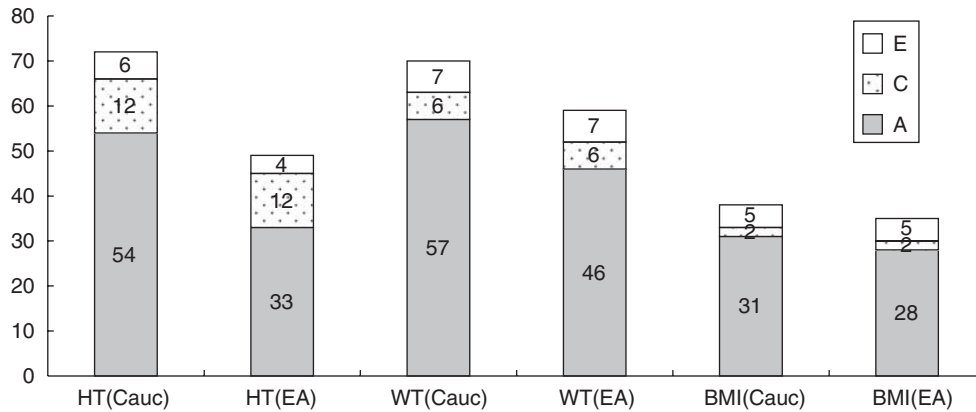
*Identification of the best-fitting models.* The procedures to identify the best-fitting models for height, weight and BMI are provided in Tables A1, A2 and A3 in the Appendix. The effects of sex-specific genes were significant for height, but not for weight or BMI. For all three body measures, A, C and E parameters were all statistically significant, perhaps because the sensitivity to detect these effects increased on account of fairly large samples used in this study and also because we did not delete any parameter unless the parameter could be removed simultaneously from both population groups. Interestingly, for all three body measures, the magnitudes of C were small and could be equated across Caucasians and East Asians without significantly worsening the model-fit. Thus, the best-fitting model for height showed that although C was equal, A and E varied across Caucasians and East Asians for both sexes. Under the best-fitting model for weight and BMI, A varied, but C was equal in Caucasians and East Asians for both sexes; and E was equal in males but not in females. Not unexpectedly, similar conclusions could be drawn when we did not log transform weight and BMI (data not shown).

*Estimates of the absolute genetic and environmental variances in the best-fitting models.* Figures 1 and 2 present the absolute variances of A, C and E for height, weight and BMI in the best-fitting models for males and females, respectively. For weight and BMI, the log-transformed values were multiplied

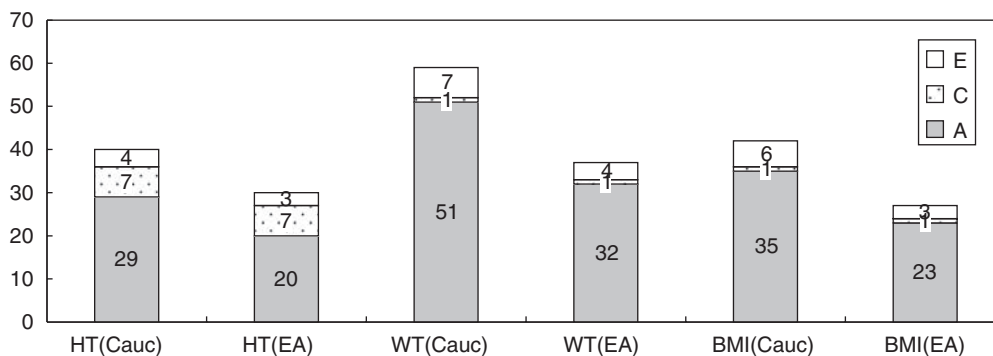
**Table 3** Maximum likelihood twin correlations and their 95% CIs for height, weight and BMI by zygosity and the population group<sup>a</sup>

	Height		Weight <sup>b</sup>		BMI <sup>b</sup>	
	East Asians	Caucasians	East Asians	Caucasians	East Asians	Caucasians
MZM	0.91 (0.90–0.93)	0.92 (0.91–0.93)	0.89 (0.86–0.90)	0.89 (0.87–0.90)	0.85 (0.82–0.87)	0.86 (0.84–0.87)
DZM	0.65 (0.54–0.73)	0.50 (0.44–0.56)	0.53 (0.40–0.64)	0.49 (0.43–0.55)	0.39 (0.25–0.52)	0.50 (0.44–0.56)
MZF	0.92 (0.90–0.93)	0.91 (0.89–0.92)	0.89 (0.87–0.91)	0.88 (0.87–0.90)	0.88 (0.86–0.90)	0.87 (0.85–0.88)
DZF	0.55 (0.43–0.65)	0.52 (0.46–0.58)	0.28 (0.12–0.42)	0.49 (0.43–0.55)	0.29 (0.13–0.43)	0.50 (0.44–0.56)
OSDZ	0.39 (0.28–0.49)	0.37 (0.31–0.43)	0.27 (0.15–0.38)	0.38 (0.31–0.44)	0.25 (0.13–0.36)	0.38 (0.31–0.44)

Abbreviations: DZF, dizygotic female twins; DZM, dizygotic male twins; MZF, monozygotic female twins; MZM, monozygotic male twins; OSDZ, opposite-sex dizygotic twins. <sup>a</sup>Age and country were treated as covariates. <sup>b</sup>Logarithmic transformation was used.



**Figure 1** Genetic (A), shared environmental (C) and nonshared environmental (E) variances of height (HT), weight (WT) and BMI in Caucasian (CAUC) and East Asian (EA) male adolescent twins in the best-fitting models.



**Figure 2** Genetic (A), shared environmental (C) and nonshared environmental (E) variances of height (HT), weight (WT) and BMI in Caucasian (CAUC) and East Asian (EA) female adolescent twins in the best-fitting models.

by 100 for an optimal presentation in figures. As we expected, for all three variables, the phenotypic variances were larger in Caucasians than in East Asians in both males and females. Notably, the magnitudes of A were consistently greater in Caucasians than in East Asians, suggesting that greater A leads to greater phenotypic variances in the former than in the latter group.

### Height

The total variance and the variances for A, C and E for height in males were, respectively, 72, 54, 12 and 6 in Caucasian adolescents and 49, 33, 12 and 4 in East Asian adolescents (Figure 1). If we decompose the difference in the total variance between the two population groups into A, C and E, then approximately 91%  $((54-33)/(72-49))$  of the difference in the total variance was attributable to the difference in A, and the remaining 9%  $((6-4)/(72-49))$  was due to the difference in E between Caucasians and East Asians. As the estimate of C was identical in the two population groups, C did not contribute to the difference in the total variance at all. When we decomposed the difference in the total variance in females into A and E, they were 90 and 10%, respectively (Figure 2). These results suggested that in both

sexes, the larger total phenotypic variances for height in Caucasians than in East Asians were largely because of greater genetic variances in the former than in the latter group. The contributions of nonshared environmental variances to differences in total variances of height were very modest.

### Weight

The total variance and the variances for A, C and E for weight in males were, respectively, 70, 57, 6 and 7 in Caucasian adolescents, and 59, 46, 6 and 7 in East Asian adolescents (Figure 1). As the C and E variances were identical in Caucasians and East Asians, the difference in the total variance between the two population groups  $(11 = 70-59)$  was entirely explained by the difference in A  $(11 = 57-46)$ .

Female data also showed that the difference in A was largely responsible for the difference in the total variance of weight between the two population groups. The total variance and the variances for A, C and E for weight in females were, respectively, 59, 51, 1 and 7 in Caucasians and 37, 32, 1 and 4 in East Asians (Figure 2). These results suggested that 86%  $((51-32)/(59-37))$  of the difference in the total variance between the two population groups was



associated with the difference in A, whereas the remaining 14% was because of the difference in E.

*BMI*

For BMI in males, the total variance, and the variances for A, C and E were 38, 31, 2 and 5 in Caucasians and 35, 28, 2 and 5 in East Asians (Figure 1). As C and E were identical between the two population groups, the difference in A accounted for 100% of the difference in the total variance between the two groups. For BMI in females, the total variance, and the variances for A, C and E were 42, 35, 1 and 6 in Caucasians and 27, 23, 1 and 3 in East Asians (Figure 2). These results indicated that 80 and 20% of the difference in the total variance between the two population groups were because of the difference in A and E, respectively.

*Estimates of relative contributions of genetic and environmental factors in the best-fitting models.* Relative contributions of A, C and E for height, weight and BMI in the best-fitting models are shown in Table 4. For all three body measures, proportions of A, C and E were similar in Caucasian and East Asian adolescents in both males and females. Heritability estimates for height, weight and BMI ranged from 75 to 81% in Caucasian male adolescents and 68 to 79% in East Asian male adolescents; shared environmental variances ranged from 5 to 16% in Caucasian males and from 6 to 24% in East Asian males; and nonshared environmental variances were between 9 and 14% in Caucasian males and between 8 and 15% in East Asian males.

Similar results were obtained from female data. Heritability estimates for height, weight and BMI ranged from 73 to 86% in Caucasians and 68 to 86% in East Asians; shared environmental variances ranged from 2 to 17% in Caucasians and from 2 to 23% in East Asians; and nonshared environmental variances were between 10 and 13% in Caucasians and between 9 and 13% in East Asians.

## Discussion

Height, weight and BMI show large variability across human populations as well as within a population. Although the causes of variations of body measures within a population are well established, the causes of variations across populations are poorly understood. To our knowledge, this study is the first to examine genetic and environmental contributions to differences in variations of height, weight and BMI between Caucasian and East Asian populations.

Our study demonstrated that although the proportions of additive genetic, and shared and nonshared environmental contributions to the variations of height, weight and BMI were similar in Caucasian and East Asian adolescents, total phenotypic variances for the three body measures were consistently and significantly greater in Caucasians than in East Asians, and these greater variances were largely

**Table 4** Relative contributions of genetic (A), shared environmental (C) and nonshared environmental (E) factors to variance in height, weight and BMI in Caucasian (CAUC) and East Asian (EA) male and female adolescent twins estimated from the best-fitting models

	Male						Female								
	Height			Weight			BMI			Weight			BMI		
	CAUC	EA		CAUC	EA		CAUC	EA		CAUC	EA		CAUC	EA	
A	0.75 (0.71–0.81)	0.68 (0.65–0.75)	0.81 (0.76–0.87)	0.77 (0.73–0.83)	0.81 (0.75–0.85)	0.79 (0.74–0.83)	0.73 (0.69–0.79)	0.68 (0.65–0.75)	0.86 (0.81–0.88)	0.86 (0.79–0.88)	0.84 (0.78–0.85)	0.83 (0.76–0.86)			
C	0.16 (0.09–0.21)	0.24 (0.15–0.28)	0.09 (0.02–0.15)	0.10 (0.02–0.16)	0.05 (0.00–0.12)	0.06 (0.00–0.12)	0.17 (0.10–0.22)	0.23 (0.15–0.27)	0.02 (0.00–0.07)	0.02 (0.00–0.10)	0.03 (0.00–0.09)	0.04 (0.00–0.12)			
E	0.09 (0.09–0.10)	0.08 (0.07–0.10)	0.10 (0.09–0.11)	0.12 (0.11–0.15)	0.14 (0.13–0.15)	0.15 (0.13–0.17)	0.10 (0.09–0.11)	0.09 (0.08–0.10)	0.12 (0.11–0.13)	0.12 (0.11–0.13)	0.13 (0.12–0.14)	0.13 (0.12–0.14)			

95% CIs are in parentheses.

attributable to greater genetic rather than environmental variations in Caucasian than in East Asian adolescents. When we divided the differences in total variances for the three body measures into additive genetic and shared and nonshared environmental components, 80 to 100% of the differences were associated with genetic variation between the two population groups.

To date, many association studies have attempted to detect genes for obesity and height, mostly with inconsistent findings and lack of replication. However, Frayling *et al.*<sup>32</sup> and Dina *et al.*<sup>33</sup> have shown that an allele in the FTO (fat mass and obesity associated) gene on chromosome 16 was associated with BMI across various European populations both in childhood and adolescence across the entire range of BMI; the homozygotes for the most significant SNP differed by about 3 kg on average. The FTO genes nonetheless accounts for only about 1% of the variance in BMI.

Consistent with prior studies,<sup>2</sup> we found evidence for sex-specific genetic effects on height in both Caucasians and East Asians. Both of the sex chromosomes have been implicated in determining height. For instance, short stature has been demonstrated in females with Turner syndrome who have only one X chromosome.<sup>34</sup> Ellis *et al.*<sup>35</sup> showed that a restriction fragment-length polymorphism in the nonrecombining centromeric region of the Y chromosome was associated with increased male height (1.9 cm). Using Caucasians and African Americans, Gudbjartsson *et al.*<sup>36</sup> identified 27 regions of the genome including a locus on X chromosome associated with height. The genes neighboring these loci were those related to biological processes for mitosis and skeletal development. Taken together, the 27 variants explained around 3.7% of the population variation in height. Recently, several studies have conducted linkage studies to locate genes for height, and found suggestive evidence for linkage on Chromosomes 6, 7, 8, 9, 12, 13, 20 and X.<sup>37–39</sup> It may be that allelic frequencies and effects of the genes involved in height, weight and BMI vary between Caucasians and East Asians, leading to differences in genetic variances for body measures between the two population groups.

Adolescence is characterized by the onset of puberty and the occurrence of growth spurts. Twins in this study were at various stages of puberty. Given substantial heritability found for timing of puberty,<sup>40</sup> one can argue that some of the differences in genetic variations for body measures observed in the present study may include genetic differences in timing of puberty between Caucasians and East Asians. However, it appears that the mean age of the onset of puberty and its variation, especially as measured by the age of menarche, are very similar in Caucasians and East Asians, with both groups showing the mean age of menarche approximately at 12.7 years (s.d. = 1.2).<sup>41–43</sup> Thus, it is unlikely that the genetic and total variance differences in body measures found in this study are because of the differences in pubertal events between Caucasians and East Asians. However, it is possible that some of the genetic variance in height, weight and BMI were confounded with

genetic variance in pubertal events, given the shared genetic variances found between body measures and pubertal measures.<sup>44</sup> Our results showed that differences in genetic/total variances of BMI between Caucasians and East Asians were greater in females than in males. These findings were in line with previous studies that demonstrated greater Asian/Caucasian differences in body fat distributions in females than in males in prepubertal children<sup>45</sup> and in adults.<sup>46</sup>

Several studies have shown low but positive assortative mating coefficients for height, weight and BMI in both Caucasian and East Asian populations.<sup>47,48</sup> Assortative mating adds to the correlation for DZ twins and can increase shared environmental influences in the classical twin design. However, it is very unlikely that the estimates of shared environmental factors in this study were significantly affected by assortative mating, given the low degree of assortative mating for height, weight and BMI. Indeed, except for height (16 to 24%), estimates of shared environmental factors in body measures in the present sample were very modest.

Crow<sup>49</sup> argued that assortative mating can cause an increase in homozygosity in a population and thereby enhance the genetic and total variance in a population. Height, weight and BMI are likely to be traits subject to directional selection in both Caucasian and East Asian populations. Because the effects of assortative mating accumulate generation after generation, even a small difference in the degree of assortative mating for height, weight and BMI between Caucasians and East Asians could produce large differences in the genetic/total variance in the long run. Thus, cumulative effects of assortative mating in conjunction with directional selection may be in part responsible for the differences in genetic/total variances for body measures between Caucasians and East Asians observed in the present study.

Another plausible explanation for the differences in genetic variation is a possible role of gene-environment interactions modeled as part of the additive genetic component in our model. That is, the higher variance for A observed in Caucasians could arise because there is a set of genes expressed only in Western environments; a likely candidate for the key environmental factors includes Western style nutrition high in energy, fat and protein. Analyzing this question in detail would require collection of twins with East Asian origin living in a Western environment. Many studies of Asian immigrants living in Western countries have demonstrated that average height, BMI and intakes of protein and fat increased with their duration of residence,<sup>50,51</sup> suggesting that environmental factors play a role in the development of obesity and physical growth.

Luke *et al.*<sup>52</sup> compared heritability of obesity-related traits using families of African diaspora who resided in a rural agricultural area in Nigeria, in the urban poor area in Jamaica and in Chicago in the United States. The authors examined whether heritability estimates vary across populations who share a common genetic background yet are exposed to vastly different environments. Heritability estimates for

weight, BMI and fat mass were similar in all three groups (approximately 50%), although heritability for height was lower in Nigeria (44%) than in Jamaica (74%) or in the United States (84%). From the similar heritability estimates found for obesity-related traits, the authors concluded that genes for obesity might exert their influences in a similar manner across a wide range of environments. A careful examination of the absolute variances of the traits published in the Luke *et al.*<sup>52</sup> study, however, provides alternative interpretations of the data. For instance, the total variance for BMI increased almost fourfold from Nigeria to the United States (13.7–50.4). The absolute genetic variances increased slightly over fourfold across the environmental gradient: 6.7 in Nigeria, 19.7 in Jamaica and 28.7 in the United States. Although the variance for height was not significantly different among the three groups, the absolute genetic variance (computed from heritability estimates in the table) rose from 39.7 in Nigeria and 48.6 in Jamaica to 71.1 in the United States. As the authors pointed out, one should note that heritability and absolute genetic variances estimated in the Luke *et al.*,<sup>52</sup> study were confounded with shared environmental influences because they used nuclear families. In spite of this limitation, the results of the Luke *et al.*<sup>52</sup> study suggest a possibility that genes for body measures might be expressed differently when exposed to different environments.

Limitations of this study need to be addressed. First, owing to low twin birth rates in East Asian countries, sample sizes for East Asian DZ twins in this study were relatively small. Thus, although there were some suggestions for nonadditive genetic effects in weight and BMI in East Asian females, we were not able to test significance of nonadditive genetic effects because detecting nonadditive genetic effects requires large twin samples.<sup>53</sup>

Secondly, the lower OSDZ twin correlation for height compared to the same-sex DZ twin correlation observed in the present study may be interpreted as the existence of sex-specific shared environmental factors rather than sex-specific genetic effects. The goodness of fit statistics (negative log-likelihood) for the full model including sex-specific shared environmental factors was the same as that for the full model including sex-specific genetic factors. Furthermore, when we removed sex-specific shared environmental effects from the full model; the difference in  $\chi^2$  was equal to that observed in the reduced model where sex-specific genetic effects were eliminated from its full model. These results suggest that the present sample does not have sufficient power to distinguish between sex-specific genetic effects and sex-specific shared environmental effects. However, given the modest size of shared environmental effects on height, sex-specific shared environmental effects are not likely to be important. Future studies should increase sample sizes, especially those for East Asian DZ twins to clearly distinguish between sex-specific genetic and sex-specific shared environmental factors in height.

Finally, the height and weight data collected from Finland, the Netherlands, South Korea and Taiwan were self-reported.

Self-reported height and weight are prone to error and bias our analyses toward lower heritability estimates and higher estimates of nonshared environmental influences.<sup>54</sup> Also variations in measurements between countries and population groups may have contributed to the differences in variances found in this study.

Our findings clearly emphasize that Caucasians and East Asians do not share all of the genetic mechanisms for height, weight and BMI. Association studies for these body measures in the future, therefore, should take account of our findings of differences in genetic variances between the two population groups.

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## Appendices

**Table A1** Model-fitting results for height<sup>a</sup>

Model description	−2LL	d.f.	Δd.f.	Δ $\chi^2$	P
Saturated Model	65 739.0	10 508			
Full sex-limitation (ACE)	65 782.0	10 560			
No sex-specific genes	65 790.5	10 562	2	8.5	0.01
A <sub>m</sub> = 0 in both CAUC and EA groups	66 449.5	10 562	2	667.5	0.00
A <sub>f</sub> = 0 in both CAUC and EA groups	66 400.1	10 562	2	618.1	0.00
C <sub>m</sub> = 0 in both CAUC and EA groups	65 796.2	10 562	2	14.0	0.00
C <sub>f</sub> = 0 in both CAUC and EA groups	65 794.9	10 562	2	12.9	0.00
A <sub>EA</sub> = A <sub>CAUC</sub> for males only	65 800.4	10 561	1	18.4	0.00
A <sub>EA</sub> = A <sub>CAUC</sub> for females only	65 788.3	10 561	1	6.3	0.01
C <sub>EA</sub> = C <sub>CAUC</sub> for males only	65 784.0	10 561	1	2.0	0.16
C <sub>EA</sub> = C <sub>CAUC</sub> for females only	65 782.1	10 561	1	0.10	0.75
E <sub>EA</sub> = E <sub>CAUC</sub> for males only	65 809.2	10 561	1	27.2	0.00
E <sub>EA</sub> = E <sub>CAUC</sub> for females only	65 819.5	10 561	1	37.5	0.00
<b>C<sub>EA</sub> = C<sub>CAUC</sub> for males and females</b>	<b>65 784.1</b>	<b>10 562</b>	<b>2</b>	<b>2.0</b>	<b>0.36</b>

Abbreviations: A, additive genetic variance; C, shared environmental variance; E, nonshared environmental variance including measurement error. Subscripts m, f, cauc, and EA represent males, females, Caucasians, and East Asians, respectively. The best-fitting model is indicated in boldface. <sup>a</sup>Age and country were treated as covariates in models.

**Table A2** Model-fitting results for weight<sup>a</sup>

Model description	−2LL	d.f.	Δd.f.	Δ $\chi^2$	P
Saturated Model	68 679.0	10 508			
Full sex-limitation (ACE)	68 725.9	10 560			
No sex-specific genes	68 727.7	10 562	2	1.8	0.41
No sex-specific genes; A <sub>m</sub> = 0 in both CAUC and EA groups	69 303.5	10 564	4	577.6	0.00
No sex-specific genes; A <sub>f</sub> = 0 in both CAUC and EA groups	69 376.8	10 564	4	650.9	0.00
No sex-specific genes; C <sub>m</sub> = 0 in both CAUC and EA groups	68 738.4	10 564	4	12.5	0.01
No sex-specific genes; C <sub>f</sub> = 0 in both CAUC and EA groups	68 731.8	10 564	4	5.9	0.21
No sex-specific genes; A <sub>EA</sub> = A <sub>CAUC</sub> for males only	68 737.8	10 563	3	11.9	0.01
No sex-specific genes; A <sub>EA</sub> = A <sub>CAUC</sub> for females only	68 745.6	10 563	3	19.7	0.00
No sex-specific genes; C <sub>EA</sub> = C <sub>CAUC</sub> for males only	68 731.1	10 563	3	5.2	0.16
No sex-specific genes; C <sub>EA</sub> = C <sub>CAUC</sub> for females only	68 731.4	10 563	3	5.5	0.14
No sex-specific genes; E <sub>EA</sub> = E <sub>CAUC</sub> for males only	68 728.9	10 563	3	3.1	0.39
No sex-specific genes; E <sub>EA</sub> = E <sub>CAUC</sub> for females only	68 771.5	10 563	3	45.6	0.00
No sex specific genes; C <sub>f</sub> = 0 in both CAUC and EA groups; C <sub>EA</sub> = C <sub>CAUC</sub> ; E <sub>EA</sub> = E <sub>CAUC</sub> for males only	68 798.2	10 567	7	72.3	0.00
<b>No sex-specific genes; C<sub>EA</sub> = C<sub>CAUC</sub> for males and females; E<sub>EA</sub> = E<sub>CAUC</sub> for males only</b>	<b>68 732.7</b>	<b>10 565</b>	<b>5</b>	<b>6.8</b>	<b>0.23</b>

Abbreviations: A, additive genetic variance; C, shared environmental variance; E, nonshared environmental variance including measurement error. Subscripts m, f, cauc, and EA represent males, females, Caucasians, and East Asians, respectively. The best-fitting model is indicated in boldface. <sup>a</sup>Age and country were treated as covariates in models.

**Table A3** Model-fitting results for BMI<sup>a</sup>

Description	-2LL	d.f.	$\Delta d.f.$	$\Delta\chi^2$	P
Saturated Model	64 280.0	10 508			
Full sex-limitation (ACE)	64 345.4	10 560			
No sex-specific genes	64 350.8	10 562	2	5.4	0.07
No sex-specific genes; $A_m = 0$ in both CAUC and EA groups	64 810.3	10 564	4	464.9	0.00
No sex-specific genes; $A_f = 0$ in both CAUC and EA groups	64 909.3	10 564	4	563.9	0.00
No sex-specific genes; $C_m = 0$ in both CAUC and EA groups	64 358.1	10 564	4	12.7	0.01
No sex-specific genes; $C_f = 0$ in both CAUC and EA groups	64 357.0	10 564	4	11.6	0.02
No sex-specific genes; $A_{EA} = A_{cauc}$ for males only	64 354.5	10 563	3	9.1	0.03
No sex-specific genes; $A_{EA} = A_{cauc}$ for females only	64 364.0	10 563	3	18.6	0.00
No sex-specific genes; $C_{EA} = C_{cauc}$ for males only	64 353.0	10 563	3	7.6	0.06
No sex-specific genes; $C_{EA} = C_{cauc}$ for females only	64 353.0	10 563	3	7.2	0.07
No sex-specific genes; $E_{EA} = E_{cauc}$ for males only	64 351.2	10 563	3	5.7	0.13
No sex-specific genes; $E_{EA} = E_{cauc}$ for females only	64 395.3	10 563	3	49.9	0.00
<b>No sex-specific genes; <math>C_{EA} = C_{cauc}</math> for males and females; <math>E_{EA} = E_{cauc}</math> for males only</b>	<b>64 354.9</b>	<b>10 565</b>	<b>5</b>	<b>9.5</b>	<b>0.09</b>

Abbreviations: A, additive genetic variance; C, shared environmental variance; E, nonshared environmental variance including measurement error. Subscripts m, f, cauc, and EA represent males, females, Caucasians, and East Asians, respectively. The best-fitting model is indicated in boldface. <sup>a</sup>Age and country were treated as covariates in models.